

Research Article

Course of HBV-infection in HIV-infected and HIV-non-infected Pregnant Women

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Abstract

The objective of the work — is to study the course of HBV-infection in pregnant women, infected and uninfected with HIV, based on the analysis of clinical-laboratory parameters.

Materials and methods. HBV-infection was diagnosed in 5.6% of women with negative HIV-status and in 9.4% positive with HIV.

To verify the diagnosis of HBV-infection, the data of anamnesis, clinical examination, laboratory tests: general clinical, biochemical, EIA, PCR, and VL in each trimester of pregnancy were used.

Results. In HIV-negative pregnant women, 71.6% of the patients were diagnosed with HBsAg carrier status and 28.4% — the replication stages. Replication stages were only in HIV-positive patients.

The frequency of clinical manifestations of CHB is higher in HIV-positive women — it is 33.33% vs 10.00% in HIV-negative ($p < 0.05$), in a significantly lower rate of cytolysis — 11.11% vs 45.00% ($p < 0.001$), which did not increase up to the childbirth. The rate of VL of HBV increased before the childbirth in 63.3% of pregnant women without HIV-infection, and in 36.7% it did not change. Thus, in 83.3% of HIV-infected, it decreased to the threshold, and in 16.7% it hasn't changed ($p < 0.01$).

During pregnancy, the immunotolerant phase of CHB in women of both groups was not transformed into immunoactive, and in HIV-negative pregnant women — the carrier status of HBsAg to the replicative form.

Conclusion. In pregnant women with HIV-infection the incidence of replicative forms of HBV-infection is 3.5 times than in pregnant women without HIV-infection, the HBsAg carrier status is not determined. HIV-immunosuppression is accompanied by the prevalence of the immunotolerant phase of CHB (88.9%) with subclinical course without disturbance of pigmentary metabolism and cytolysis increase against the background of a decrease of VL HBV up to the threshold in 83.3% ($p < 0.01$). The inverse weak correlation between the level of CD4 + T-lymphocytes and VL HBV was determined.

In HIV-negative pregnancies, latent forms of HBV-infection prevail (71.6%). Replicative forms are characterized by a low degree (80.0%) of HBV viremia ($p < 0.05$) with minimal cytolysis in 43.3% of women ($p < 0.001$), which did not change during pregnancy.

Keywords

HBV-infection; co-HIV-infection; pregnant women

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Problem statement and analysis of the latest research

Under present conditions HBV-infection is one of the most urgent medical and social problems in many countries of the modern world, as it is a frequent cause of chronic liver disease, and in women of childbearing age it can be realized as perinatal infection. This problem is common to midwives, infectious disease physicians, pediatricians and requires a general strategy for the management of a pregnancy in such women [1, 3, 5]. Knowledge of the natural course of HBV-infection in pregnant women will help to understand the pathogenetic mechanisms of its negative impact on maternal and fetal health. Timely diagnosis of viral hepatitis in pregnant women, establishing their clinical form is essential for the prognosis and prevention of obstetric and perinatal complications.

In recent years an increase in viral hepatitis in pregnant women co-infected with HIV is observed. In this regard it is important to study the characteristics of the course of CHB on the background of HIV-infection.

According to the recommendations of the WHO and the European Association for the Study of Liver Diseases, pregnancy is not contraindicated for the women with HBV-infection who have not reached the stage of cirrhosis, as well as in the absence of signs of active inflammatory process in the liver or cholestasis because it does not have a negative effect on the course of CHB [5, 8, 9]. The feature of HBV-infection in HIV-infected pregnant women is the latent course in 32.7-43.9% [1, 2].

Therefore, a comprehensive clinical and laboratory examination during pregnancy should play a decisive role in the formulation and verification of the diagnosis, which will enable to study the risk factors that contribute to perinatal

infections of the fetus.

The purpose of the work is to study the course of HBV-infection in pregnant women infected and uninfected with HIV, based on the analysis of clinical and laboratory parameters.

1. Materials and Methods

For the period from 2012 to 2017 the progression of HBV-infection in pregnant women aged 18-35, depending on their HIV-status was analyzed. Out of the 3762 pregnant women with negative HIV-status, 211 women infected with HBV were found, accounting for 5.6 % of the total number of examined pregnant women. During examination of 192 pregnant women with positive HIV-status, chronic hepatitis B infection (CHB) was diagnosed in 18 women, which is accounted for 9.4 %.

For the verification of the diagnosis of HBV-infection with the establishment of its clinical stage and phase, data from anamnesis of the disease, clinical examination by organs and systems, laboratory tests (general and clinical), immunoassay (ELISA), polymerase chain reaction (PCR), qualitative and quantitative – viral load (VL), instrumental methods of investigation (ultrasound of the abdominal cavity of the pregnant woman) were used. Among the main criteria the indexes of the replicative activity of the virus and the activity of the inflammatory process in the liver according to the indicators of the content of ALT, AST, bilirubin and its fractions in serum and thymol samples in each trimester of pregnancy were evaluated.

The dynamics of these indicators was studied, depending on the trimester of pregnancy and the degree of HIV-related immunosuppression.

Women, in which during registration in women's consultation, HBsAg was detected during initial screening, were tested for the final diagnosis in the following volume: HBeAg, anti-HBeAg, anti-HBcor IgM and IgG, anti-HBcor total and anti-HBsAg by the immunoassay method (ELISA). In repeated studies in the dynamics of pregnancy (in the 2nd and 3rd trimesters) anti-HBsAg, anti-HBeAg and anti-HBcor IgG were detected to exclude acute HB in the recent past. In women with positive serological markers, HBV DNA was determined by PCR method – qualitative and quantitative (VL HBV) in each trimester of pregnancy.

When HBsAg, anti-HBeAg and anti-HBcor IgG were detected in the absence of other markers of hepatitis and cytolysis syndrome and at the threshold level of VL HBV or less than 10^4 copies/ml, women were verified as HBsAg-carriers. There were no clinical and anamnestic data before the pregnancy that could indicate the benefit of HBV-infection in these women.

The replicative stage of the disease was established based on the detection of HBsAg, HBeAg, anti-HBcor (total), positive PCR of HBV DNA and the presence of cytolysis syndrome. In 15 (7.1 %) women the replication stages of HBV-infection with mutated strains were diagnosed, in which other positive replicating markers were determined in the absence of HBeAg.

Laboratory examinations of pregnant women with positive HIV-status were performed on the basis of a centralized laboratory of diagnosis of HIV-infection, toxoplasmosis, venereal diseases and viral hepatitis, certified by the Ministry of Health of Ukraine, at the Ivano-Frankivsk Oblast Clinical Infectious Disease Regional Center for HIV/AIDS Prevention, and women with negative HIV-status were screened at the Synevo Laboratory.

The probability of a possible error for each indicator was determined by the statistical criterion of the Student. The statistical processing of the results of the research was carried out on a personal computer using the prevailing database of surveyed patients in the program STATISTICA for Windows 6.0. The average values (M) were calculated, the average errors of the arithmetic mean (m). To determine the relationship between values, the Pearson rank correlation method was used to calculate the correlation coefficient (r).

2. Results and Discussion

Most often among HIV-negative pregnant women HBsAg carrying was diagnosed as an integrative stage of HBV-infection – 151 (71.6 %), significantly rarer replicative stage – 60 (28.4 %): in immune active phase – 27 (45.0 %) and in immune tolerant phase – 33 (55.0 %) (Table 1).

All HIV-positive pregnant women were diagnosed only with replication stages: in immune tolerant phase – 16 (88.9 %) and in immune active phase – 2 (11.1 %), HBsAg carrying was not registered in any case.

The frequency of clinical manifestations of replicative forms of chronic HBV-infection in pregnant women is presented in Table 2.

More often there were no complaints during pregnancy in pregnant women with HIV-negative status in contrast to women with HIV-positive status – 38.33 % vs 16.67 % ($p < 0.05$).

Among the clinical manifestations of chronic HBV-infection during the gestation period increased fatigue and decreased appetite were observed reliably less often in pregnant women in the first group – 35.00 % and 21.67 % respectively, unlike in pregnant women in the second group – 61.11 % and 50.00 % respectively ($p < 0.05$).

In women without HIV-infection nausea and periodic heaviness in the right hypochondrium were also significantly less common in 23.33 % and 10.00 % respectively, especially after meals that could be linked to pregnancy, whereas in pregnant women with positive HIV-status – 50.00 % and 33.33 % respectively ($p < 0.05$). These complaints disturbed women mainly in the 1 and 2 trimesters of gestation and until the end of pregnancy were present only in 10.00 % of pregnant women in the 1 group and 33.33 % in the second group ($p < 0.05$).

Hepatomegaly was observed only in 10.00 % of women in the 1 group in contrast to 33.33 % in the comparison group ($p < 0.05$), which is three times more often and may be also linked to the administration of HAART, smoking, the use of alcohol and drugs. In all women of the two groups with the immune active phase of HBV-infection no disturbances

Table 1. Variants of the course of HBV-infection in pregnant women depending on the HIV-status

	Stages and phases of chronic HBV-infection	The number of pregnant women			
		HIV-negative status		HIV-positive status	
		absolute numbers	%	absolute numbers	%
1	HBV-infection:	211	100	18	100
1.1	HBsAg carrying (integration stage)	151	71.6	-	-
1.2	replication stage of HBV infection:	60	28.4	18	100
	- immune active phase	27	45	2	11.1
	- immune tolerant phase	33	55	16	88.9

Table 2. The frequency of clinical manifestations of replicative forms of HBV-infection in pregnant women depending on HIV-status

Clinical manifestations	Pregnant women			
	1st group HIV-negative status, n=60		2nd group HIV-positive status, n=18	
	absolute numbers	%±m	absolute numbers	%±m
Increased fatigue	21	35.00±6.16	11	61.11±11.49*
Decreased appetite	13	21.67±5.32	9	50.00±11.79*
Periodic nausea	14	23.33±5.46	9	50.00±11.79*
The heaviness in the right hypochondrium	6	10.00±3.87	6	33.33±11.11*
Hepatomegaly	6	10.00±3.87	6	33.33±11.11*
No complaints	23	38.33±6.28	3	16.67±8.78*

Notes.

* – the probability of discrepancy between indicators in pregnant women of the 1 and 2 groups, $p < 0.05$.

of pigmentary metabolism were observed in the presence of hepatomegaly during the entire gestation period. Normal indexes of thymol test, absence of hypergammaglobulinemia indicated also a lack of mesenchymal-inflammatory response in women of these groups.

It should be noted that not all women were timely screened in the first trimester of pregnancy: among HIV-negative women only 70.0 % of women and among HIV-positive women – 61.1 % due to untimely access to women's consultation and registration in connection with pregnancy (Table 3).

The minimum degree of cytolysis ($ALT = 64.0 \pm 2.4$ U/l, $AST = 58.0 \pm 3.6$ U/l) was observed in 43.3 % of women in the 1st group with the immune active phase of HBV-infection and in women in the 2nd group only in 11.1 % of cases throughout the whole gestation period ($p < 0.001$). There was no marked increase in cytolysis before delivery in women of both groups, even with a high degree of viremia ($VL_{HBV} > 10^5$ copies/ml).

Moderate degree of cytolysis in women with HIV-positive status was not detected. Only one case (1.7 %) was observed in woman with HIV-negative status during the 2nd-3rd trimesters of pregnancy on the background of low VL_{HBV} (1.2×10^2 copies/ml).

During pregnancy cytolysis was not observed in 55.0 % of women with immune tolerant phase of HBV-infection and

negative HIV-status compared to 88.9 % of pregnant women with HIV-positive status ($p < 0.001$).

Particular attention should be paid to the fact that the immune tolerant phase of chronic HBV-infection was not transformed into immune active throughout the pregnancy in women of both groups and in women with HIV-negative status the HBsAg-carrying was not transformed into the replicative stage.

In pregnant women with HIV-negative status (Table 4) the replication stage of HBV-infection was usually accompanied by a low degree of viremia of HBV ($VL \leq 10^5$ copies/ml) with its growth on 1-2 log in the third trimester compared with the second trimester – 80.0 % vs. 61.7 % ($p < 0.05$). In women with HIV-positive status, on the contrary, there was a decrease in the viral load of HBV before childbirth – low level of viremia was detected in 61.1 % in the second trimester against 16.7 % in the third trimester ($p < 0.05$).

A high degree of viremia ($VL > 10^5$ copies/ml) with a growth on 2-3 log was diagnosed in 16.7 % of pregnant women of the 1st group in the third trimester compared with 5.0 % in the second trimester ($p < 0.05$). In women of the second group high degree of viremia was not registered.

In women without HIV-infection threshold degree of viremia ($VL \leq 750$ copies/ml) was significantly more often registered in the second trimester of pregnancy than in the third trimester

Table 3. Degree of hepatitis activity in pregnant women with replicative forms of HBV-infection depending on HIV-status

Degree of cytolysis	Terms of examination of pregnant women					
	1group			2 group		
	HIV-negative status, n=60			HIV-positive status, n=18		
	I trimester	II trimester	III trimester	I trimester	II trimester	III trimester
	abs./%	abs./%	abs./%	abs./%	abs./%	abs./%
Minimum	18/30.0	26/43.3	26/43.3	1/5.5	2/11.1	2/11.1*
Low	-	-	-	-	-	-
Moderate	-	1/1.7	1/1.7	-	-	-
High	-	-	-	-	-	-
Absent	24/40.0	33/55.0	33/55.0	10/55.6	16/88.9	16/88.9*
Total	42/70.0	60/100.0	60/100.0	11/61.1	18/100.0	18/100.0

Notes.

* – the probability of discrepancy between the indicators in pregnant women of the 1 and 2 groups in the third trimester of pregnancy, $p < 0.001$.

Table 4. Degree of viremia in pregnant women with replicative forms of HBV-infection depending on the HIV-status

Degree of viremia	Terms of examination of pregnant women					
	1group			2group		
	HIV-negative status, n=60			HIV-positive status, n=18		
	I trimester	II trimester	III trimester	I trimester	II trimester	III trimester
	abs./%	abs./%	abs./%	abs./%	abs./%	abs./%
≤ 750 copies/ml	12/20.0	20/33.3	2/3.3 *	6/33.3	7/38.9	15/83.3***●
$\leq 10^5$ copies/ml	15/25.0	37/61.7	48/80.0**	5/ 27.8	11/61.1	3/16.7***●
$> 10^5$ copies/ml	-	03.05.2000	10/16.7**	-	-	-
Total	42/70.0	60/100.0	60/100.0	11/61.1	18/100.0	18/100.0

Notes.

* – the probability of the discrepancy between the indicators in pregnant women of the 1st group in the 2 and 3 trimester of pregnancy, $p < 0.01$;

** – the probability of the discrepancy between the indicators in pregnant women of the 1group in the second and third trimester of pregnancy, $p < 0.05$;

*** – the probability of the discrepancy between the indicators in pregnant women of the 2nd group in the 2 and 3 trimester of pregnancy, $p < 0.01$;

● – the probability of the discrepancy between the indicators in pregnant women of the 1 and 2 groups in the third trimester of pregnancy, $p < 0.01$.

of pregnancy – 33.3 % vs. 3.3 % ($p < 0.05$), which means that before childbirth it grew. In women with HIV/HBV coinfection VL HBV, on the contrary, declined: in the second trimester of pregnancy the threshold level of the viremia was registered in 38.9 % of patients and in the third trimester – 83.3 % ($p < 0.05$).

However, in rare cases in women of the 1 group, such a regularity was not observed. In 2 women (3.3 %), on the contrary, the low degree of viremia ($VL = 10^4$ copies/ml) in the second trimester decreased to the threshold degree in the third trimester with normal ALT levels during pregnancy. It should be noted that in women with HIV-negative status, in contrast to women with HIV-positive status, the level of

viremia increased before childbirth. In the 3 trimester the threshold level of the viremia was in 3.3 % of women in first group against 83.3 % of the second ($p < 0.01$), which is probably due to the administration of lamivudine, which is included in the treatment scheme of HIV-infection and at the same time inhibits the replication of the HBV.

Analyzing the course of hepatitis in women with HIV-positive status, we took into account the dependence of VL HBV on the level of HIV-related immunosuppression. The level of $CD4+T$ -lymphocytes > 500 cells/ μ l was estimated as normal, 350-499 cells/ μ l – moderate immunosuppression, 200-349 cells/ μ l – expressed immunosuppression, < 200 cells/ μ l – deep immunodeficiency according to Order

No. 182 (Table 5).

In pregnant women co-infected with CHB/HIV statistically insignificant dependence of the VL HBV on the degree of HIV-immunosuppression ($p=0.572$) was noted according to the critical value of the Student's t-distribution.

The Pearson correlation coefficient is determined between the two data groups – CD4+T-lymphocytes and VL HBV in these women. The inverse weak correlation between the investigated values is established (the correlation coefficient (r) is -0.142).

In pregnant women with different degree of immunosuppression the varying levels of VL HBV were found almost at the same frequency. Only one woman with VL HBV $\leq 10^5$ copies/ml was in a stage of deep immunodeficiency.

According to the current research data HBV-infection in pregnant women usually runs in a chronic asymptomatic form (97.4 %). Therefore, its diagnosis is difficult in pregnant women. Regarding subclinical forms of replicative HBV-infection, they are accompanied by asthenic (90.0-93.0 %), dyspeptic (35.0-40.0 %), mesenchymal-inflammatory (32.0-36.0 %), cholestatic syndromes (20.0-25.0 %), hepatosplenomegaly (35.0-40.0 %) and also by insignificant impaired liver function, manifested with a minimal degree of cytolysis in 50.0-52.0 % of patients [5, 6, 8]. The above data coincide with the results of our study.

Also, the results of our study, as well as the data of studies by other authors, indicate that despite the replication of the virus cytolysis rates remained within the normal range throughout the pregnancy in part of pregnant women (48.0-50.0 %). At the same time occasional cases of progressive deterioration of the liver function up to the development of fulminant hepatic failure in HBsAg-positive pregnant women are described in the literature [4, 5, 9].

According to the observations of other authors, during pregnancy in women with CHB thymol test increases, level of serum transaminases decreases on the background of normal level of bilirubin, the amount of blood circulating virus decreases, which may be observed due to the changes in the immune reactivity of the body of pregnant women and due to the increase of estrogens concentration in plasma [6, 7, 8].

Perevertenij L. U. and co-authors (2014) point to a high replication of the HBV in the first trimester of pregnancy, followed by its reduction before delivery in 28.0 % of women [5]. Chuikova K. I. and co-authors (2011), vice versa, investigated the increase of the level of viral replication to 36 weeks of gestation, which coincides with our data [6].

In literature available to us we did not find the analysis of maternal HBV-infection on the background of HIV in pregnant women.

3. Conclusions

In pregnant women with HIV-infection the incidence of replicative forms of HBV-infection is 3.5 times higher in comparison with pregnant women without HIV-infection, the HBsAg-carrying is not determined. HIV-immunosuppression in preg-

nant women with HIV-infection is accompanied by a predominance of the immune tolerant phase of CHB (88.9 %), which is characterized by a subclinical course without disturbing the pigmentary metabolism and the growth of cytolysis before childbirth on the background of a decrease HBV viremia to the threshold in 83.3 % of cases ($p<0.01$). The inverse weak correlation was established between the level of CD4+T-lymphocytes and VL HBV.

In pregnant women not infected with HIV, latent forms of HBV-infection are prevalent in the form of HBsAg carrying (71.6 %). Replicative forms were characterized by a low level (80.0 %) of HBV viremia before delivery ($p<0.05$) with minimal cytolysis in 43.3 % of women ($p<0.001$), which did not change throughout the whole gestation period.

4. Prospects of further research

Prospects of further research will be directed at studying the risk factors that contribute to perinatal infections of the fetus.

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Table 5. Degree of viremia of HBV in HIV-positive pregnant women with CHB, depending on the degree of immunosuppression

Number of CD4+T-lymphocytes	Viral load of HBV in pregnant women, n=18					
	≤ 750 copies/ml		≤ 105 copies/ml		>105 copies/ml	
	absolute numbers	%	absolute numbers	%	absolute numbers	%
>500 cells/ μ l	3	16.7	2	11.1	-	-
350-499 cells/ μ l	3	16.7	4	22.2	-	-
200-349 cells/ μ l	2	11.1	3	16.7	-	-
<200 cells/ μ l	-	-	1	5.6	-	-

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